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Selective Pulmonary and Systemic Vasodilator Effects of Amrinone in Children: New Therapeutic Implications

BRADLEY W. ROBINSON, MD, HENRY GELBAND, MD, FACC, MADELEEN S. MAS, MD, FACC
Miami, Florida

Objectives. The present study was performed to determine the systemic and pulmonary hemodynamic effects of amrinone in infants and children with a cardiac left to right shunt to determine if there is a beneficial effect on the pathophysiology of this condition.

Background. Amrinone is a bipyridine derivative with inotropic and vasodilator effects that have not been systematically evaluated in the pediatric patient with increased pulmonary blood flow.

Methods. Nineteen patients (aged 2 months to 8.3 years) with one or more left to right shunts were evaluated during cardiac catheterization with direct hemodynamic measurements made before and 10 min (peak effect) after administration of a bolus injection of amrinone, 3 mg/kg body weight. The Fick method was used to calculate pulmonary and systemic blood flow, and resistances were then calculated.

Results. In group A, five patients with normal pulmonary artery pressure and resistance, amrinone significantly reduced mean pulmonary artery pressure by 19%, mean left atrial pressure by 39% and systemic vascular resistance by 17%. In group B, seven patients with pulmonary artery hypertension (mean pulmonary artery pressure >20 mm Hg) and normal pulmonary vascular resistance (total pulmonary resistance ≤3 Wood U·m^2), amrinone significantly reduced the pulmonary artery pressure by 27%, systolic aortic pressure by 5%, mean aortic pressure by 12%, pulmonary arteriolar resistance by 36% and total pulmonary vascular resistance by 26%. In group C, seven patients with pulmonary artery hypertension (mean pulmonary artery pressure >20 mm Hg) and elevated pulmonary vascular resistance (total pulmonary resistance >3 Wood U·m^2), amrinone significantly reduced the pulmonary arteriolar resistance by 49%, total pulmonary resistance by 47% and pulmonary arteriolar/systemic vascular resistance ratio by 45% and increased the heart rate by 15%.

Conclusions. In children with a cardiac left to right shunt, amrinone 1) appears to have selective vasodilator effects depending on the pulmonary artery pressure and resistance, 2) has a beneficial hemodynamic effect in children with normal pulmonary artery pressure and resistance, and 3) may have a role in the treatment of patients with pulmonary artery hypertension without causing systemic hypotension.

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Children with a large cardiac left to right shunt are frequently encountered in the practice of pediatric cardiology and cardiovascular surgery. Although digoxin and diuretic agents have provided the primary mode of pharmacotherapy for decades, many investigators challenge their effectiveness because the underlying pathophysiologic features result in symptoms that may represent pulmonary circulatory congestion rather than myocardial contractile failure. Still, there are both anecdotal and objective data to support the benefits of such therapy (1).

These pathophysiologic features led to the suggestion that vasodilators may have a beneficial role in the clinical setting by lowering systemic vascular resistance, resulting in increased cardiac output and decreased pulmonary blood flow. This hypothesis has been supported in multiple studies (2–8) using several vasodilating agents in both humans and animals with a large left to right shunt.

Amrinone is a nonglycoside, noncatecholamine bipyridine derivative that possesses both potent positive inotropic and systemic vasodilating effects. Its mechanism of action involves selective inhibition of phosphodiesterase III that indirectly results in an increase in intracellular cyclic adenosine monophosphate production (9).

The present study was performed to evaluate the in vivo hemodynamic effects of amrinone on the pathophysiology of left to right shunts in children and to determine whether this agent may be of benefit in the clinical setting.

Methods

Study patients. The study group consisted of 19 patients, 2 months to 8.3 years old, with a left to right shunt. There were 9 girls and 10 boys and 8 had trisomy 21. The left to right cardiac shunts consisted of, alone or in combination, atrial septal defect, ventricular septal defect, endocardial cushion defect or patent ductus arteriosus (Table 1).

All patients were maintained on combinations of digoxin,

From the Division of Cardiology, Department of Pediatrics, University of Miami School of Medicine, Miami, Florida.

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Address for correspondence: Madeleen S. Mas, MD, Pediatric Cardiology (R-76), Department of Pediatrics, University of Miami, School of Medicine, Box 016960, Miami, Florida 33101.

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Table 1. Patient Clinical Data

Pt No.	Age (mo)/ Gender	Diagnosis	Wt (kg)	Treatment Dig	Diu	Cp
		Group A: Normal PAP + TPR				
1	45/M	VSD	17.1	–	–	–
2	6/M	ECD	7.6	+	+	–
3	12/M	VSD	8.2	+	–	–
4	100/M	ASD/VSD	31.0	–	–	–
5	4/F	VSD	5.0	+	+	–
		Group B: PAH + TPR ≤3 Wood U·m^2				
6	2/F	ECD/PDA/Tri21	2.9	+	+	–
7	6/M	VSD	5.4	+	+	–
8	7/F	ECD/Tri21	5.5	+	+	–
9	8/M	VSD	6.1	+	+	–
10	2/M	VSD/PDA per Tri21	4.0	+	+	+
11	10/M	VSD	6.8	+	+	–
12	6/F	VSD	5.0	+	+	–
		Group C: PAH + TPR >3 Wood U·m^2				
13	13/M	ECD/Tri21	8.1	–	–	–
14	11/F	ECD/Tri21	6.4	+	+	–
15	14/F	VSD	7.9	+	–	–
16	3/F	ECD/Tri21	3.3	+	+	–
17	3/M	VSD/Tri21	4.8	+	+	+
18	3/F	PDA/VSD per Tri21	4.0	–	–	–
19	7/F	VSD	5.0	+	+	–

ASD = atrial septal defect; Cp = captopril; Dig = digoxin; Diu = diuretics (furosemide or spironolactone); ECD = endocardial cushion defect; F = female; M = male; PAH = pulmonary artery hypertension; PAP = pulmonary artery pressure; PDA = patent ductus arteriosus; Pt = patient; TPR = total pulmonary resistance; Tri21 = trisomy 21; VSD = ventricular septal defect; Wt = weight.

diuretic drugs or afterload reducers. Four patients (Patients 1, 4, 13 and 18) did not receive any medication. All medications were held 12 h before the study. The study was approved by the Institutional Human Research Committee, and informed consent was obtained from the patients' parents before the study.

Patients received either meperidine, promethazine hydrochloride or chlorpromazine intramuscularly or chloral hydrate orally as premedication. One patient received midazolam intravenously as premedication. All patients were studied in the fasting state and in the supine position.

All patients underwent percutaneous right and left heart catheterization. Amrinone was given as a bolus 3 mg/kg body weight, infusion at a rate of 1 mg/s into the pulmonary artery in 17 patients; during the early stage of the study, the bolus was infused into the left ventricle of 1 patient and into a peripheral vein in another. Heart rate and the following pressure data were obtained before and 10 min after the amrinone bolus dose: aortic (systolic and mean), main pulmonary, left atrial or pulmonary capillary and right atrial. Using the same protocol, oxygen saturation (by Waters Oxicom 2000) was measured in the superior vena cava, left atrium or pulmonary capillaries, main pulmonary artery and aorta. Pulmonary and systemic flow were calculated using the Fick method and indexed for body surface area. The pulmonary/systemic flow (Q_p/Q_s) ratio, systemic vascular resistance, total pulmonary vascular resistance, pulmonary arteriolar resistance, pulmonary arteriolar resistance/systemic vascular resistance ratio, volume of left to right shunt and stroke volume were then calculated. Oxygen consumption was measured accurately in 15 of 19 patients by the continuous flow-through method using the Waters MRM-2 instrument (10) and was assumed in the remaining four patients. Cardiac angiography was not performed until all hemodynamic data had been obtained. Platelet count and liver function tests were obtained after completion of the study, and amrinone plasma levels were obtained within 10 to 25 min after the initial bolus to ensure therapeutic levels.

Pulmonary artery hypertension was defined as a mean pulmonary artery pressure >20 mm Hg (11) and elevated total pulmonary resistance as >3 Wood U·m^2 (12). Five patients with a mean control pulmonary artery pressure ≤20 mm Hg and total pulmonary resistance ≤3 Wood U·m^2 were assigned to group A; seven with a mean control pulmonary artery pressure >20 mm Hg and total pulmonary resistance ≤3 Wood U·m^2 to group B, and seven with a mean pulmonary artery pressure >20 mm Hg and control total pulmonary vascular resistance >3 Wood U·m^2 to group C.

Statistics. The Student *t* test for paired observation was used to compare differences between control and postdrug mean values. A p value < 0.05 was considered significant. All values were reported as mean value ± SD.

Results

Group A (normal pulmonary artery pressure and resistance). In group A, amrinone significantly reduced mean pulmonary artery pressure by 19% (from 15.6 ± 3.4 to 12.6 ± 2.8 mm Hg, $p < 0.05$), left atrial mean pressure by 39% (from 5.6 ± 1.5 to 3.4 ± 1.7 mm Hg, $p < 0.05$) and systemic vascular resistance by 17% (from 17.1 ± 5.4 to 14.2 ± 3.7 Wood U·m^2, $p < 0.05$). Although there were small decreases in pulmonary flow index (9%), volume of left to right shunt (14%) and Q_p/Q_s ratio (16%), and a small increase in systemic flow index (5%), these differences were not significant. There were no significant changes in mean or systolic aortic pressure, pulmonary arteriolar resistance, total pulmonary resistance, pulmonary arteriolar resistance/systemic vascular resistance ratio, heart rate, stroke volume and oxygen consumption (Table 2).

Group B (increased pulmonary artery pressure and normal resistance). In group B, amrinone significantly reduced the mean pulmonary artery pressure by 27% (from 37 ± 7.8 to 27 ± 4.8 mm Hg, $p < 0.005$), systolic aortic pressure by 5% (from 78 ± 5.3 to 74 ± 6.2 mm Hg, $p < 0.05$), mean aortic pressure by 12% (from 57 ± 4.0 to 50 ± 2.0 mm Hg, $p < 0.05$), pulmonary arteriolar resistance by 36% (from 1.4 ± 0.4 to 0.9 ± 0.3 Wood U·m^2, $p < 0.05$) and total pulmonary

Table 2. Summary of Data

	Group A (normal PAP + TPR)			Group B (PAH + TPR ≤3 Wood U·m²)			Group C (PAH + TPR >3 Wood U·m²)		
	Control	Peak Am	Δ%	Control	Peak Am	Δ%	Control	Peak Am	Δ%
Flow									
Q_s (liters/min per m²)	4.1 ± 1.1	4.3 ± 1.1	↑ 5	3.8 ± 1.5	4.5 ± 2.7	↑18	3.2 ± 0.8	3.3 ± 0.9	↑ 3
Q_p (liters/min per m²)	16.1 ± 11	14.7 ± 9.4	↓ 9	20.8 ± 7.1	22.2 ± 8.3	↑ 7	7.9 ± 2.9	12.5 ± 6.5	↑58*
Q_p/Q_s	3.8 ± 2.3	3.2 ± 1.6	↓16	5.9 ± 2.3	5.6 ± 2.1	↓ 5	2.5 ± 0.7	4.0 ± 2.1	↑60
$Q_{l\to r}$	12.1 ± 10	10.4 ± 8.3	↓14	16.9 ± 6.7	17.7 ± 6.6	↑ 5	4.7 ± 2.4	9.1 ± 6.5	↑94*
Pressure (mm Hg)									
PA mean	15.6 ± 3.4	12.6 ± 2.8	↓19*	37.0 ± 7.8	27.0 ± 4.8	↓27*	54.9 ± 15	42.7 ± 15	↓22*
Ao mean	67.0 ± 8.4	58.8 ± 5.7	↓12	57.0 ± 4.0	50.0 ± 2.0	↓12*	65.4 ± 13.0	63.3 ± 11	↓ 3
Ao systolic	96.6 ± 13.9	79.4 ± 6.6	↓18	77.6 ± 5.3	73.6 ± 6.2	↓ 5*	87.1 ± 14.6	83.1 ± 12.8	↓ 5
LA mean	5.6 ± 1.5	3.4 ± 1.7	↓39*	8.9 ± 2.0	7.6 ± 1.9	↓15	7.9 ± 3.0	7.3 ± 3.9	↓ 8
Resistance									
PAR (Wood U·m²)	1.0 ± 0.7	1.0 ± 0.9	—	1.4 ± 0.4	0.9 ± 0.3	↓36*	6.7 ± 2.9	3.4 ± 2.0	↓49*
TPR (Wood U·m²)	1.54 ± 1.1	1.35 ± 1.0	↓12	1.9 ± 0.6	1.4 ± 0.5	↓26*	7.8 ± 3.3	4.1 ± 2.3	↓47*
SVR (Wood U·m²)	17.1 ± 5.4	14.2 ± 3.7	↓17*	15.5 ± 5.0	13.2 ± 6.0	↓15	19.9 ± 4.6	18.7 ± 4.8	↓ 6
PAR/SVR	0.05 ± 0.03	0.07 ± 0.04	↑40	0.10 ± 0.05	0.09 ± 0.04	↓10	0.33 ± 0.13	0.18 ± 0.10	↓45*
Other									
SV (ml/beat)	18.9 ± 10	17.7 ± 8.6	↓ 6	9.2 ± 4.3	10.3 ± 6.4	↑12	6.9 ± 1.9	6.8 ± 3.3	↓ 1
Heart rate (beats/min)	114 ± 15	127 ± 22	↑11	125 ± 9	133 ± 19	↑ 6	144 ± 13	165 ± 21	↑15*
VO_2 (ml/min per m²)	178 ± 66	198 ± 56	↑11	219 ± 68	220 ± 76	—	170 ± 33	189 ± 30	↑17

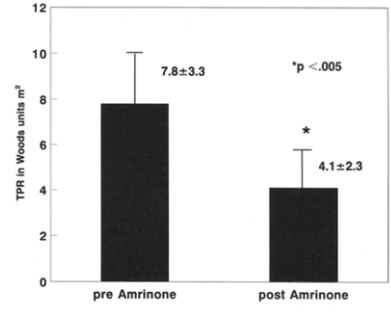
*$p < 0.05$ compared with control subjects (paired t test). Unless otherwise specified values are mean value ± SD. Ao = aortic; Δ% = percent change; LA = left atrium; PA = pulmonary artery; PAR = pulmonary arteriolar resistance; Peak Am = peak amrinone effect; $Q_{l\to r}$ = net volume of left to right shunt index; Q_p = pulmonary flow index; Q_s = systemic flow index; SV = stroke volume; SVR = systemic vascular resistance; VO_2 = oxygen consumption; other abbreviations as in Table 1.

resistance by 26% (from 1.9 ± 0.6 to 1.4 ± 0.5 Wood U·m², $p < 0.05$). Although the mean values showed an overall decrease in QP/QS ratio, this ratio increased after amrinone administration in Patients 6, 7 and 8, with left to right shunt volume increasing in Patients 7 and 8. Systemic flow index, pulmonary flow index, left atrial mean pressure, systemic vascular resistance, pulmonary arteriolar/systemic vascular resistance ratio, stroke volume, heart rate or oxygen consumption did not change significantly in group B (Table 2).

Group C (increased pulmonary artery pressure and resistance). In group C, amrinone significantly reduced the pulmonary artery pressure by 22% (from 54.9 ± 15 to 42.7 ± 15 mm Hg, $p < 0.005$), pulmonary arteriolar resistance by 49% (from 6.7 ± 2.9 to 3.4 ± 2.0 Wood U·m², $p < 0.005$); total pulmonary resistance by 47% (from 7.8 ± 3.3 to 4.1 ± 2.3 Wood U·m², $p < 0.005$ [Fig. 1]) and pulmonary arteriolar/systemic vascular resistance ratio by 45% (from 0.33 ± 0.13 to 0.18 ± 0.10, $p < 0.005$). As expected with a decrease in pulmonary vascular resistance, pulmonary flow index increased significantly by 58% (from 7.9 ± 2.9 to 12.5 ± 6.5 liters/min per m², $p < 0.05$); and the volume of left to right shunt increased by 94% (from 4.7 ± 2.4 to 9.1 ± 6.5 liters/min per m², $p < 0.05$); the Q_p/Q_s ratio increased by 60% (p = NS). Heart rate increased significantly by 15% (from 144 ± 13 to 165 ± 21 beats/min, $p < 0.005$). There were no significant changes in systemic flow index, mean or systolic aortic pressure, mean left atrial pressure, systemic vascular resistance, stroke volume or oxygen consumption (Table 2).

Oxygen consumption. This variable was measured accurately in all except Patients 2, 6, 10 and 12. In group A, after amrinone administration, oxygen consumption increased from 3% to 65%. In group B, the oxygen consumption response was variable, increasing in two patients and decreasing in two; in three patients, oxygen consumption was not measured. In

Figure 1. Mean total pulmonary resistance before (pre) and after (post) amrinone infusion in the seven patients in group C (high levels of pulmonary artery pressure and total pulmonary resistance). Note the significant decrease after administration of amrinone.



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group C, oxygen consumption increased in five patients, decreased in one patient and did not change in one patient.

Amrinone plasma levels. These levels were obtained in 10 of the 19 study patients. Values obtained 10 to 25 min after amrinone administration ranged from 2.2 to 7.5 μg/ml, levels previously reported (9) to be in the therapeutic range.

Postdrug platelet count and liver function tests. These were performed in 14 of 19 patients. Patients 1 and 15 had mild elevation of aspartate aminotransferase (69 and 57 U/liter, respectively [normal 0 to 40]) after amrinone infusion. Platelet counts remained normal. There were no other significant complications, although Patient 1 had a 4-min episode of junctional rhythm associated with transient hypotension 15 min after amrinone infusion.

Discussion

The role of digoxin and diuretic agents in the treatment of infants who are symptomatic from a large cardiac left to right shunt remains controversial. Vasodilators have been used in these patients in an attempt to decrease the degree of left to right shunting and thereby increase systemic output, improving oxygen delivery to the tissues. We hypothesized that amrinone may act in a similar manner with the added benefit of a direct inotropic action.

Selective hemodynamic effects of amrinone. In this study, amrinone had beneficial hemodynamic effects in patients with normal pulmonary artery pressure and normal total pulmonary resistance; amrinone significantly reduced the left atrial mean pressure, systemic vascular resistance and pulmonary artery pressure. The decrease in left atrial mean pressure presumably resulted from the positive inotropic or the afterloading effects of amrinone because pulmonary blood flow did not decrease significantly.

In patients with pulmonary artery hypertension and normal total pulmonary resistance, amrinone had different vasodilator effects. In these patients, the group most commonly seen clinically, amrinone decreased pulmonary artery pressure by 27%, total pulmonary resistance by 26%, systolic aortic pressure by 5% and mean aortic pressure by 12%. Thus, pulmonary flow did not change significantly to increase the degree of the left to right shunt. However, in three of seven patients the Q_p/Q_s ratio did increase, indicating a possible detrimental effect of amrinone in this group.

Most important, in patients with elevated pulmonary artery pressure and elevated total pulmonary resistance, amrinone decreased the total pulmonary resistance, resulting in an increase in pulmonary blood flow, Q_p/Q_s and left to right shunt volume.

Overall in the three groups, the results indicate that amrinone may have selective vasodilator properties depending on the magnitude of pulmonary artery pressure and resistance. In patients with normal pulmonary artery pressure and total pulmonary resistance, amrinone reduced the systemic vascular resistance to a greater degree than it reduced total pulmonary resistance. In patients with elevated pulmonary artery pressure, amrinone reduced pulmonary arteriolar resistance more than it reduced systemic vascular resistance in both the normal and high pulmonary vascular resistance groups but the reduction was much greater in the high total pulmonary resistance group (Fig. 2). In this group of patients, amrinone may have a striking beneficial effect that has obvious important clinical significance.

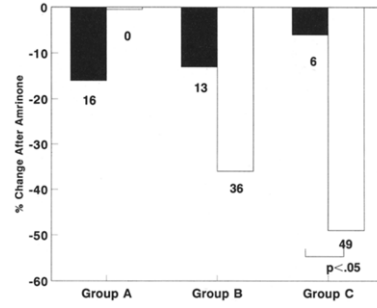

Figure 2. Percent decrease in mean resistance after amrinone infusion in the three patient groups. **Solid bars** represent systemic vascular resistance and **open bars** show pulmonary arteriolar resistance. Note the inverse relation between the decrease in systemic versus pulmonary vascular resistance from group A (normal levels of pulmonary artery pressure and total pulmonary resistance) to group C (high levels of pulmonary artery pressure and total pulmonary resistance). In group C, amrinone decreased pulmonary vascular resistance much more than it decreased systemic vascular resistance, whereas the reverse was true in group A. See text for discussion.

Previous investigations. Data are scant regarding the effects of amrinone on the pulmonary circulation. Amrinone may relax vascular smooth muscle by altering calcium transport and intracellular calcium release by a mechanism that is unclear at the present time. It has been shown to relax vascular smooth muscle (13), bovine intrapulmonary arteries and to decrease pulmonary arteriolar resistance in newborn lambs with pulmonary hypertension (14). In patients with pulmonary hypertension awaiting heart transplantation, Deeb et al. (15,16) showed that intravenous amrinone therapy decreased both pulmonary artery pressure and resistance. In the present study, amrinone selectively vasodilated the pulmonary circulation in patients depending on the degree of pulmonary artery pressure and resistance.

New therapeutic implications. Patients with pulmonary artery hypertension and elevated pulmonary vascular resistance pose difficult management problems. These patients are often considered inoperable unless their increased pulmonary vascular resistance is reversible. Oxygen therapy is currently administered in the catheterization laboratory to

determine reversibility of elevated pulmonary vascular resistance (17). Patients with a total pulmonary resistance >8 Wood U·m² are considered inoperable (18). However, in this study, amrinone decreased the total pulmonary vascular resistance into an operable range in three patients. Amrinone may be an ideal agent to add to a catheterization laboratory protocol in evaluating patients with elevated pulmonary vascular resistance due to one or more cardiac left to right shunts.

Of paramount importance, amrinone may have an important therapeutic role in the management of patients with a reactive pulmonary circulation. Although amrinone is currently used in the postoperative period, its effects are believed to be attributed to its inotropic and systemic vasodilator action. Berner et al. (19) reported the administration of amrinone to eight children after cardiac surgery for both left to right shunts and mitral valve replacement and concluded that amrinone acted primarily as a systemic vasodilator. In contrast, in our study, amrinone appeared to have selective vasodilator effects depending on the degree of pulmonary artery pressure and resistance. Although amrinone may be useful in patients with a normal pulmonary artery pressure and normal pulmonary vascular resistance, these patients rarely pose significant management problems. Furthermore, amrinone may not be useful and even contraindicated in patients with a high pulmonary artery pressure and high pulmonary flow left to right shunt physiology who are symptomatic because of pulmonary overcirculation. However, our data suggest that amrinone may have a new, beneficial role in patients with high pulmonary vascular resistance and low pulmonary flow physiology. These patients historically pose the most difficult management problems and account for significant morbidity and mortality from reactive pulmonary hypertension in the postoperative period (20). In this group, amrinone may effectively decrease pulmonary vascular resistance without causing serious systemic hypotension. These findings have important therapeutic implications in the management of such problematic patients that are commonly encountered in the practice of pediatric cardiology and cardiovascular surgery.

Further prospective trials evaluating the oral bipyridine derivative milrinone, which has been shown to have hemodynamic effects similar to those of amrinone with fewer side effects, seem warranted to assess whether this agent will be beneficial in long-term management of the patient with elevated pulmonary vascular resistance (21).

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